DOI:
10.1016/j.diabet.2017.12.007

Document Version
Peer reviewed version

Accepted Manuscript

Title: Intensive lifestyle modifications with or without liraglutide 3mg *vs* sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!–<RunningTitle>Medical *vs* surgical weight-loss programme</RunningTitle>–>

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PII: S1262-3636(17)30589-X
DOI: https://doi.org/doi:10.1016/j.diabet.2017.12.007
Reference: DIABET 964

To appear in: *Diabetes & Metabolism*

Received date: 2-9-2017
Accepted date: 19-12-2017

Please cite this article as: Capristo E, Panunzi S, De Gaetano A, Raffaelli M, Guidone C, Iaconelli A, L'Abbate L, Birkenfeld AL, Bellantone R, Bornstein S, Mingrone G, Intensive lifestyle modifications with or without liraglutide 3mg *vs* sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!–<RunningTitle>Medical *vs* surgical weight-loss programme</RunningTitle>–>, *Diabetes and Metabolism* (2017), https://doi.org/10.1016/j.diabet.2017.12.007

without liraglutide 3 mg *vs* sleeve gastrectomy: A three-arm non-randomized, controlled, pilot study<!--<RunningTitle>Medical *vs* surgica

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linically eligible subjects choose to undergo surgical treatment for obesity, other options should be investigated. This study aimed to assess
g liraglutide daily *vs* sleeve gastrectomy (SG) on BMI after 1 year.

d at an Italian university hospital, non-diabetic patients eligible for bariatric surgery were recruited from a weight-loss clinic and had the op
tion of 25 subjects in each arm matched by BMI and age. ILM consisted in 813 kcal of a very low-calorie diet (VLCD) for 1 month, followe
ns plus 30 min of brisk walking daily and at least 3 h of aerobic exercise weekly. SG patients followed a VLCD for 1 month and a free diet

led; retention was 100% in the SG and 85% in the two medical arms. SG reduced BMI by 32% ($P < 0.001$ *vs* medical arm), while ILM + li
y ($P < 0.001$). More women allocated themselves to the ILM + liraglutide group. Weight loss was 43 kg with SG, 26 kg with ILM + liraglu
h SG, −6.3 kg with ILM and −8.3 kg with ILM + liraglutide. Prevalence of prediabetes was significantly lower with ILM + liraglutide, and
d SG *vs* 39% by ILM alone. Cardiometabolic risk factors were greatly reduced in all three groups.

aglutide 3.0 mg once daily associated with drastic calorie-intake restriction and intensive physical activity promoted a 24% weight loss, wh
with SG, while preserving lean body mass. Although this study was non-randomized, it was designed to explore the efficacy of medical tr

surgery; Lifestyle modifications; Liraglutide; Obesity; Very low-calorie diet

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diseases such as type 2 diabetes (T2D) and cardiovascular disease (CVD) [1–3]. The number of people affected by morbid or class-III obe
he US, contributed to 20% of the total per capita healthcare expenditures in 2000 [5].

or > 35 kg/m^2 in the presence of obesity complications, are eligible for bariatric surgery [6]. In the face of low mortality rates—0.08% with
benefits, including reduction of long-term mortality [8] and T2D remission [9–11]. However, due to the public's perception as well as thos
cedure, in fact, only 1% of clinically eligible subjects choose to undergo surgical treatment for obesity [12].

ble for bariatric surgery yet who are neither willing nor able to undergo the operation should, however, be offered other therapeutic options.
intensive lifestyle modification (ILM) intervention with or without a 3-mg daily liraglutide injection *vs* sleeve gastrectomy (SG) with free
whom were eligible for bariatric surgery, was on a voluntary basis: they were invited to choose their own allocation to one of the three arms

LP)-1 analogue approved for the treatment of obesity at a dose of 3 mg/day and marketed under the name Saxenda, has been proven to reduc
kg in patients taking a placebo [13]. More important, this weight reduction was maintained for up to 3 years, as shown by le Roux et al. [14
atients who wish to be considered for bariatric surgery.

calorie diet (VLCD) has been reported to allow weight loss of around 20 kg in men and nearly 16 kg in women [15]. However, the weight-r
thods to maintain weight loss. One possible option is a low-carbohydrate, high-fat, high-protein diet, which has been associated with releva
ccretion of lean body mass [16,17]. Therefore, our present pilot study started with a VLCD for the first month to match the diet usually pres
t, high-protein diet over the subsequent 11 months to achieve substantial weight loss.

an operation widely performed worldwide, it has earned its place as a primary bariatric operation [18]. Similarly, the regimen of a VLCD f
vith anti-obesity drugs such as orlistat [19] and sibutramine [20]. Indeed, this dietary combination was recently proposed for the Diabetes R
programme is delivered in a routine primary-care setting to T2D patients to achieve long-lasting normoglycaemia [21].

and the medical options for treatment of morbid obesity beyond bariatric surgery.

IODS

of the Catholic University Hospital in Rome, Italy, and eligible for bariatric surgery were given the option to choose any one of three possi
nd matched for BMI and age. The basic design of the study is shown in Fig. 1. Patients were also informed that, while they had to pay for li
n any case, all patients in the medical arms were also offered the possibility to undergo surgery on completion of the study.

mmittee of our institution, and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidel
nd an additional written informed consent was signed before SG surgery.

baseline BMI at 1 year, while secondary endpoints were changes at 1 year from baseline in weight, body composition, plasma glucose, hor
lipid profile and modification of dysglycaemia. The study was conducted between 2 November 2015 and 31 January 2017. Inclusion criteri
BMI > 40 kg/m^2, or > 35 kg/m^2 if one or more comorbidities (hypertension, sleep apnoea, severe hip or knee arthritis) were present. Exclusio
ry of pancreatitis, or major depressive or other severe psychiatric disorders; and family or personal history of multiple endocrine cancers or

vent 1 month of a VLCD with 813 kcal/day [3 × 200 mL Fortimel (Nutricia Advanced Medical Nutrition, Schiphol, The Netherlands) = 60
90 kcal; and All-Bran cereal (50 g; Kellogg Company, Battle Creek, MI, USA) = 123 kcal, 20 g of fibre], followed by an LCD (12 kcal/kg
months together with intensive physical exercise (30 min/day of brisk walking plus at least 3 h/week of aerobic exercise) with or without 3 m
starting at a dose of 0.6 mg and followed by weekly 0.6-mg increments up to 3.0 mg to reduce side-effects.

ically prescribed and paid for by the patients. Also, patients were evaluated at baseline and at 1, 3, 6, 9 and 12 months after starting the inter
physicians every week to report any weight changes, the frequency and intensity of their exercise as well as any side-effects, and received

h involves longitudinal resection of the stomach along its greater curvature, with complete excision of the fundus and part of the body and a
lt is a vertical tube-shaped gastric ‘sleeve’ with a capacity of approximately 100 mL.

patients followed the same dietary regimen as those in the medical arms: 813 kcal/day of a VLCD. During the subsequent 11 months, they
dietitian at each follow-up visit. Patients were evaluated at baseline and at 1, 3, 6, 9 and 12 months after starting the intervention.

using calibrated scales, and with subjects wearing light clothing and no shoes. Body composition was measured by dual-energy X-ray abso
rovides results for both lean body mass (LBM) and fat mass (FM).

ure (DBP) were measured twice by an experienced nurse with patients sitting and rested. Hypertension was defined as SBP ≥ 140 mmHg a

ine and at the 6-month and 1-year follow-up visits, using the Community Healthy Activities Model Program for Seniors (CHAMPS) questi
physical activities over a typical week over the past 4 weeks and the corresponding time spent, quantified into broad categories (< 1 h, 1–2.

od samples were obtained at baseline and at each visit to determine plasma glucose, insulin and serum lipoprotein concentrations.

glucose oxidase method (Analox Sensor Technology, Stokesley, North Yorkshire, UK) and plasma insulin by microparticle enzyme immu
IU/mL and an intra-assay coefficient of variation (CV) of 6.6%. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycer
lipoprotein (LDL) cholesterol was calculated with the Friedewald formula [23]. HDL cholesterol was defined as low if < 40 mg/dL (1.0 m

e HOMA-IR index [24], which is calculated by multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), then dividing it b

l as numbers and percentages, and continuous data as the mean ± standard deviation (SD); categorical data were analyzed
ariance (ANOVA). Changes in continuous variables at 1 year are expressed in both absolute terms and percentages relativ
100. ANOVA was used to test differences across the three groups, and pairwise post-hoc comparisons were performed by
ver time in weight, BMI, LBM and FM were analyzed by means of a linear mixed-effects model, and the carry-forward m
sidered statistically significant, and all analyses was performed with RStudio open-source software.

.3% male) were grouped into three study arms (Fig. 1). The chi-squared test indicated a significant ($P = 0.025$) imbalance in the allocations
ddition, at the time of enrolment, statin drugs were being used by 12/25 patients in the SG group *vs* 6/25 patients in the ILM and 7/25 in the
bserved in total and LDL cholesterol (Table I).

etection of T2D, geographical distance and the cost of liraglutide. In addition, 10 subjects (four in the ILM group and six in the ILM + lirag
lt the intervention was too rigid, while two patients in the ILM + liraglutide group left the study because they considered the drug too exper

l two because they were relocated for work. However, because data from at least two follow-up visits were available (Fig. 2), all recruited

composition

ear follow-up was 975.16 ± 106.27 kcal/day, corresponding to 10.95 ± 1.74 kcal/kg body weight, whereas the caloric intakes in the two me
t significantly different in the three arms, baseline weight in the SG group (133.5 ± 18.58 kg) was significantly higher than in the other two
de groups, respectively; $P < 0.001$ for both pairwise comparisons), most likely due to the greater number of men in the surgical group. Patie
65.26 ± 11.39) than the other two groups [ILM and ILM + liraglutide = 45.16 ± 6.06 kg and 55.76 ± 10.92 kg, respectively ($P < 0.001$ *vs* b
nificantly higher in the SG than in the other two groups (Table I). Values at baseline and for all the recorded variables at 1 year, as well as t
s a good reflection of the absolute variations in anthropometric parameters.

ble I) was recorded in the SG group (−32.15 ± 4.11%), and the smallest weight decrement was recorded in the ILM patients (−14.12 ± 5.09
23.65 ± 8.03% ($P < 0.001$ for ILM *vs* ILM + liraglutide; $P < 0.001$ for ILM *vs* SG; and $P < 0.001$ for SG *vs* ILM + liraglutide). Using a mix
roup than in the ILM group (β interaction term for time × treatment = −0.56; $P < 0.001$). Likewise, BMI was more decreased over time in b
eatment = −0.62 ± 0.04 and −0.32 ± 0.05 ($P < 0.001$ for both respectively)].

ents was significantly different from the trend in the ILM group (β for time × treatment = −0.49, $P < 0.001$). Results for the FM absolute Δ
groups.

of BMI, body weight, LBM and FM in the three groups. Changes in BMI (kg/m^2) and weight (kg) over time are depicted in Fig. S1 (see sup

MA-IR

l three groups: −6.87 ± 2.34, −17.85 ± 7.88 and −11.08 ± 9.88 in the ILM, ILM + liraglutide and SG groups, respectively (ILM + liraglutid
ng insulin decreased more in the ILM + liraglutide and SG groups than in the ILM group ($P < 0.001$ for both pairwise comparisons). Simila
groups with significantly larger decrements seen with ILM + liraglutide ($P < 0.001$) and with SG ($P < 0.001$) than with ILM (−34.05 ± 8.4
ps, respectively).

ILM, 7 (20%) in the ILM + liraglutide and 15 (43%) in the SG group— had impaired fasting glucose (IFG) at baseline, defined by the Ame
ients (82.86%) normalized their baseline glycaemia at 1 year to values < 100 mg/dL, while fully normalized fasting glycaemia was observe
/15) of the SG subjects.

groups were recorded for total, LDL and HDL cholesterol and TG at baseline (Table I). TG decreased over time in all three groups, with the
t in the SG group: −23.48 ± 12.34%, −31.08 ± 17.84% and −14.12 ± 27.04% in the ILM, ILM + liraglutide and SG groups, respectively, wi
.02). Total and LDL cholesterol also decreased in all patients. The average changes in total cholesterol were −9.76 ± 5.18, −15.01 ± 11.46 a
with a significant difference ($P = 0.003$) between the ILM and SG groups. LDL cholesterol was reduced by −10.5 ± 11.1, −22.3 ± 14.4 and
with a significant difference ($P = 0.04$) again between ILM and SG groups. On the other hand, while HDL cholesterol increased by 9.62 ±
ely, it decreased in the SG group (−1.58 ± 31.26%), with significant post-hoc associations between ILM + liraglutide *vs* ILM ($P = 0.02$) and

o significant differences among them, and a similar DBP decrease was observed in the ILM and ILM + liraglutide groups (the post-hoc co

oup experienced severe nausea and vomiting within 1 to 3 months of enrolment, while two patients were referred for constipation. In additi

tion

size necessary to demonstrate non-inferiority [25] of 3-mg liraglutide treatment compared with SG was calculated. Assuming a non-inferio
r words, hypothesizing the worst-case scenario for our pilot study (4% SD for SG and 8% SD for liraglutide)—the sample size necessary to
M compared with SG had to include 88 subjects. Allowing for an attrition rate of 20%, the total number of subjects to be enrolled in a rando

g liraglutide 3 mg/day to an ILM programme results in a remarkable BMI change at 1 year, albeit lower than that achieved with SG. While
24% and ILM reduced it by 14%. Thus, liraglutide as an add-on therapy to ILM almost doubled the effect of dietary restriction and physica

t 11.6 kg of LBM due to rapid weight loss, low protein intakes and virtually no physical exercise, whereas LBM was considerably better pr
and ILM groups, respectively), which followed a high-protein diet and intensive physical activity. However, the percentage of LBM reducti

programme was much higher than that observed in a 1-year RCT [13] wherein the mean change in body weight with liraglutide 3 mg was, c
style-modification approaches involved. Indeed, while the 1-year RCT diet was restricted to 500 kcal/day and patients were given only a re
mme [13], in our pilot series, subjects followed a VLCD for 1 month and a strict 12 kcal/kg body weight high-protein, high-fat, low-carbohy
hysical-activity programme.

markable compared with other appetite-suppressing drugs. After 4 weeks of a VLCD, sibutramine maintained a 1-year weight loss of −5.2 ±
ent study, those receiving ILM + liraglutide 3 mg lost 26.25 ± 10.65 kg over the same period of time.

xone 16 mg plus sustained-release bupropion 360 mg/day led to a weight reduction of −5.0 ± 0.3% ($P < 0.0001$ *vs* placebo) whereas, in ou
6]. In fact, the latter treatment led to considerably better results than phentermine/topiramate 7.5 mg/46 mg and 15 mg/92 mg by mouth, wh
ared with 1.2% with placebo ($P < 0.0001$ for both phentermine plus topiramate doses) [27].

100% in the surgical arm and 84% in the two medical arms. Liraglutide caused gastrointestinal side-effects in two out of 25 patients, while
g.

was significantly lower in the ILM + liraglutide group than in the two other groups. Insulin resistance, as evaluated by HOMA-IR, was redu
n the ILM group. Circulating TG fell by 31% in the ILM + liraglutide group, while the reduction was by 23% and 14% in the ILM and SG

a cholesterol was observed in the SG arm (−22%), the most pronounced increase of HDL cholesterol (27%) was in those receiving ILM + l
so, it was noted that, unlike other authors [28], our SG patients showed no improvement in HDL cholesterol, possibly as a consequence of t
le counselling was offered to our surgical patients to more closely simulate what actually happens in real life after bariatric surgery. Althou
weight-loss surgery, the vast majority of patients fail to do them.

hree study arms, whereas DBP was significantly reduced only in the ILM + liraglutide group. Overall, weight loss was associated with a net

288) for SG in Italy is €5681, while the cost of Saxenda is €4320 (€360/month × 12) per year, with a net difference of €1361 in favour of S
re are as yet no data on long-term (≥ 5 years) 3-mg liraglutide weight-loss effects.

randomization methodology, which may have generated selection bias. Indeed, there was an imbalance between the number of women allo
ever, our study design did most likely reflect the preferences of men and women, and of the wealthy and non-wealthy, for either medical or
e liraglutide arm because they either preferred a less-invasive approach to obesity than men or were more willing to pay the high cost of the
Health Service (SSN). Other limitations were the short duration of our trial (1 year) and that it was a single-centre study.

dy did not include cut-off values for dyslipidaemia and arterial blood pressure. Eligible patients were enrolled as they were, with no effort
While this had no direct implication for the primary study endpoint, it may have influenced secondary outcome measures.

gators in designing drug and bariatric surgery trials are multiple. Apart from common obstacles such as approval from ethics committees an
g with bariatric surgery in a country where the latter is fully covered by the SSN, while the former is totally paid for by the patients themsel
with bariatric operations and with liraglutide injections were explained, many of our patients decided to go with liraglutide. Thus, a well-de
ebo and/or ILM + SG could offer new insights into possible alternatives to bariatric surgery, particularly for those who are either unwilling

wn that, at least over the short term, injectable liraglutide at a dose of 3.0 mg once daily in association with a drastically restricted caloric in
s around twice that achieved with ILM alone and only 25% less than with SG. In addition, the sample size necessary for an RCT to detect n
mg daily and SG was calculated to be 110 (55 in each arm). Such a randomized study appears to be necessary in light of the gender-biased
d also has the potential to expand our medical options for treating morbid obesity in addition to bariatric surgery. Indeed, the effect of lirag
vious 1-year RCT [13], probably because of our more stringent dietary regimen and the associated intensive physical-activity programme.

ly. EC, MR and LLA acquired the data. The data analysis was done by SP and ADG. Interpretation of the data was by EC, GM, MR, SP, R
SB and AB made a critical revision. All authors approved the final version of the manuscript. EC, GM and SP ensured that questions relate
estigated and resolved.

t.

nternal funds of the Catholic University and by a grant from Deutsche Forschungsgemeinschaft (DFG) to GM, SRB and ALB (IRTG 2251).

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ve lifestyle modification; VLCD: very low-calorie diet; LCD: low-calorie diet; SG: sleeve gastrectomy.

ment and outcomes.

rom baseline in body mass index (BMI; kg/m^2), body weight, lean body mass (LBM) and fat mass (FM) in the three study arms. Data are m
eve gastrectomy.

llow-up, expressed as the percent delta (% Δ) and absolute Δ in the three study treatment groups

	ILM + liraglutide 3 mg		**Sleeve gastrectomy (SG)**		
	(n = 25)		**(n = 25)**		
3 (52)	M: 5 (20)	F: 20 (80)	M: 14 (56)	F: 11 (44)	***P* = 0.025***
					Tukey's HSD test
					ILM *vs* ILM + liraglutide / **ILM *vs* SG** / **ILM + liraglutide *vs* SG**
SD	**Mean**	**SD**	**Mean**	**SD**	***P*** / ***P*** / ***P***
0.78	46.2	17.35	42.7	11.74	0.548 / 0.989 / 0.632
.65	40.77	5.20	42.88	5.46	0.48 / 0.05 / 0.25
.16	31.05	4.36	28.98	2.96	0.03 / < 0.001 / 0.15
.09	–23.65	8.03	–32.15	4.11	< 0.001 / < 0.001 / < 0.001
.98	–9.75	3.69	–13.91	3.13	< 0.001 / < 0.001 / < 0.001
4.21	109.65	19.06	133.5	18.58	0.93 / < 0.001 / < 0.001
6.62	83.4	14.81	90.07	9.62	0.006 / 0.30 / 0.22
.09	–23.65	8.03	–32.15	4.11	< 0.001 / < 0.001 / < 0.001
5.9	–26.25	10.65	–43.43	10.47	< 0.001 / < 0.001 / < 0.001
1.36	53.89	11.65	68.23	14.54	0.002 / 0.84 / < 0.001
0.82	45.61	10.95	56.61	9.98	< 0.001 / 0.51 / 0.001
.26	–15.26	9.03	–16.05	8.24	0.03 / 0.008 / 0.90

.86	–8.28	5.71	–11.62	7.44	0.49	0.005	0.10
.06	55.76	10.92	65.26	11.39	< 0.001	< 0.001	0.002
.82	39.4	9.06	34.12	8.83	0.36	0.70	0.08
8.6	–28.36	15.13	–47.59	10.65	0.06	< 0.001	< 0.001
.78	–16.36	9.38	–31.15	9.21	0.005	< 0.001	< 0.001
.46	5.44	0.54	5.63	0.45	0.08	0.67	0.38
0.3	4.39	0.42	4.99	0.47	< 0.001	0.08	< 0.001
.34	–17.85	7.88	–11.08	9.88	< 0.001	0.15	0.01
.14	–0.97	0.46	–0.64	0.58	< 0.001	0.13	0.04
3.9	173.86	89.28	196.24	89.02	0.99	0.49	0.57
2.63	52.03	18.21	59.86	17.53	< 0.001	< 0.001	0.39
.49	–65.07	15.99	–64.16	15.58	< 0.001	< 0.001	0.97
2.46	–129.36	84.21	–136.37	78.64	< 0.001	< 0.001	0.93
.36	6.3	3.49	7.33	3.24	0.93	0.68	0.47
.84	1.55	0.59	2.01	0.67	< 0.001	< 0.001	0.09
8.4	–71.19	14.36	–68.38	13.38	< 0.001	< 0.001	0.73
.95	–5.02	3.23	–5.33	2.86	0.001	< 0.001	0.91
0.64	1.96	0.50	1.54	0.78	0.001	< 0.001	0.06
0.41	1.31	0.41	1.27	0.69	0.002	< 0.001	0.96
2.34	–31.08	17.84	–14.12	27.04	0.48	0.28	0.02
0.54	–0.63	0.43	–0.27	0.46	0.99	0.03	0.04
.52	5.87	1.26	4.56	0.68	0.24	0.001	< 0.001
.27	4.82	0.68	3.48	0.67	0.99	< 0.001	< 0.001
.18	–15.01	11.46	–22.43	17.02	0.39	0.003	0.13
.31	–0.99	0.92	–1.07	0.84	0.13	0.04	0.92
.14	0.98	0.1	1.1	0.32	0.04	0.85	0.16
0.1	1.26	0.19	1.02	0.27	0.91	0.002	< 0.001
1.6	27.44	11.16	–1.58	31.26	0.02	0.19	< 0.001
0.1	0.27	0.12	–0.07	0.36	0.06	0.03	< 0.001
.51	3.99	1.11	2.8	0.56	< 0.001	0.2	< 0.001

.38	2.97	0.65	1.9	0.6	0.39	< 0.001	< 0.001
1.1	–22.3	14.4	–29.4	25.22	0.12	0.002	0.42
.35	–1.02	0.82	–0.9	0.73	0.1	0.02	0.85
4.2	81.6	8	81.6	10.27	0.24	0.24	0.99
.63	79.6	6.6	81.2	5.64	0.77	0.95	0.56
.25	–2.15	5.88	0.79	12.74	0.51	0.06	0.44
.86	–2	4.78	–0.4	10.29	0.5	0.14	0.69
.07	125.8	15.72	130.6	14.74	0.01	0.3	0.41
.22	122.2	11.19	124.6	10.3	0.02	0.19	0.64
.32	–2.42	5.25	–3.83	9.89	0.64	0.97	0.74
.64	–3.6	7.57	–6	13.23	0.67	0.99	0.64

l-study value – baseline value)/baseline value × 100;
female; HSD: honest significant difference; HOMA-IR: homoeostasis model of assessment of insulin resistance; HDL/LDL: high-density/low-density lipoprotein

s index (BMI) and body weight in patients in the three study arms. ILM: intensive lifestyle modification; SG: sleeve gastrectomy.